# DOUBLE-BLIND STUDY OF BOTULINUM TOXIN IN SPASMODIC TORTICOLLIS

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*Summary* In a double-blind trial in 21 patients with spasmodic torticollis botulinum-A toxin produced both subjective and objective improvement, including significant pain relief in 14 of the 16 patients presenting with pain. Side-effects were more frequently reported during placebo administration and no significant systemic adverse reactions were noted.

## Introduction

SPASMODIC torticollis remains an enigma, like other forms of primary dystonia. There are conflicting accounts of basal-ganglia pathology in the disorder.[1-3] Positron emission tomography has demonstrated a breakdown in the normal linkages of energy consumption in the brain,[4] and there has been a suggestion that the abnormal muscle activity of torticollis persists, at an attenuated level, during sleep.[5] Treatment is difficult and inadequate, partly because the underlying mechanism is unknown. Medical management gives unpredictable results, the usual approaches to pharmacotherapy being administration of anticholinergics, antidopaminergics, dopaminomimetics, and drugs that modify serotonin or γ-aminobutyric acid.[6] Attempts to achieve symptomatic relief with central muscle relaxants have been disappointing. Surgical approaches seldom result in sustained benefit and may cause irreversible damage: procedures involving the brain can lead to disturbances of speech, and those involving the nerve roots, nerves, or muscles can result in mutilating asymmetric distortion of the cervical anatomy.

Local injection of botulinum-A toxin has been used successfully in the treatment of several ophthalmological disorders—concomitant strabismus,[7] endocrine orbital myopathy,[8] and lateral rectus paralysis.[9] If given in the correct dose at the correct location, it reduces the force of the unwanted muscle contraction without producing weakness; its action usually lasts 6–8 weeks. Botulinum-A toxin has also been used to treat hemifacial spasm[10] and blepharospasm.[11] In our pilot study on the use of botulinum toxin in spasmodic torticollis,[12] the safety and efficacy of injections into neck muscles were assessed. We report here a double-blind study that was undertaken to extend our previous findings.

## Patients and Methods

21 patients (8 men, 13 women) were included in the study; their ages ranged from 34 to 72 years (50·0 ± 12·3 SD). The mean disease duration was 9·4 years (±9·0 SD). 1 patient had generalised dystonia, 1 segmental involvement (oromandibular dystonia, blepharospasm, and writer's cramp), and 1 blepharospasm with torticollis. Each patient was given two treatments 3 months apart, one containing 100 mouse units (equivalent to 40 ng) of botulinum-A toxin diluted in 1 ml of normal saline, and the other containing 1 ml of normal saline without any toxin. The order of the injections was randomised, and both the patient and the physician giving the injections were "blind".

The sternomastoid, splenius capitis, and trapezius muscles were surveyed for clinical and electromyographic spasms, and the most active two were chosen for treatment. Injections (0·25 ml) were made at two sites in each of the two selected muscles. Videotape recordings were made of each patient before and 6 weeks after each treatment. At the end of the study the videotape recordings were assessed "blind" by a second physician. Scores were assigned according to the following scale:

*(A) Amplitude of sustained movements*
Rotation: 0 = absent, 1 = < 15°, 2 = 15–30°, 3 = > 30°.
Tilt: 0 = absent, 1 = < 15°, 2 = 15–30°, 3 = > 30°.
Ant/Retr: 0 = absent, 1 = mild, 2 = moderate, 3 = severe.
Combined score = A.

*(B) Duration of sustained movements*
1 = intermittent, 2 = constant.

*(C) Shoulder elevation*
0 = absent, 1 = mild and intermittent,
2 = mild and constant, or severe and intermittent,
3 = severe and constant.

*(D) Tremor*
Severity: 1 = mild, 2 = severe.
Duration: 1 = occasional, 2 = continuous.
Severity × Duration = D.

*Total score* = [(A) × (B)] + (C) + (D).

The randomised videotape recordings were again scored "blind" by another physician, and the inter-observer variability was determined.

Patients were seen 10 days and 6 weeks after each treatment and were asked about local or general weakness and any other new symptoms. They were asked to record body temperature on 3 consecutive days after each injection. Subjective improvement, especially pain relief, was also noted at each visit.

## Results

3 patients withdrew from one arm of the study because of lack of effect—2 during the botulinum toxin phase and 1 during the placebo phase. In consequence, 19 patients received botulinum toxin (of whom 16 had pain associated with the torticollis) and 20 received normal saline (of whom 17 had pain).

A. H. MACLENNAN AND OTHERS: ACKNOWLEDGMENTS AND REFERENCES—*continued*

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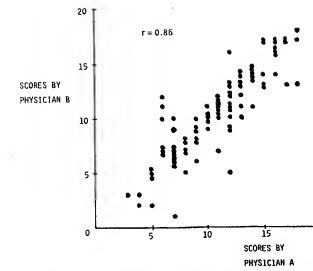


**Scores on torticollis (88 observations) by two "blind" physicians using a clinical scoring protocol.**

TABLE I—TORTICOLLIS SCORE BEFORE AND AFTER INJECTIONS

| Patient | Botulinum toxin | | Normal saline | |
|---|---|---|---|---|
| | Before | After | Before | After |
| 1 | 15 | 17 | 12 | 15 |
| 2 | 12 | 4 | 5 | 5 |
| 3 | 8 | 12 | " | " |
| 4 | 12 | 12 | 11 | 13 |
| 5 | 6 | 4 | 13 | 7 |
| 6 | 10 | 5 | 6 | 10 |
| 7 | 14 | 12 | 12 | 14 |
| 8 | 11 | 10 | 10 | 5 |
| 9 | 15 | 12 | 16 | 17 |
| 10 | " | " | 16 | 12 |
| 11 | 13 | 7 | 10 | 11 |
| 12 | 11 | 7 | 11 | 11 |
| 13 | 13 | 7 | 13 | 5 |
| 14 | 15 | 9 | 14 | 13 |
| 15 | 14 | 14 | 14 | 7 |
| 16 | 3 | 3 | 7 | 8 |
| 17 | 16 | 16 | 15 | 14 |
| 18 | " | " | 16 | 18 |
| 19 | 7 | 7 | 9 | 11 |
| 20 | 8 | 7 | 6 | 7 |
| 21 | 7 | 4 | 6 | 13 |

*Validation of Scale*

The differences between scores assigned by the two "blind" physicians are shown in the figure. The correlation coefficient was 0·86.

*Efficacy*

The changes in the clinical scores are shown in table I. There was a significant ($p < 0·05$) fall in the torticollis scores after botulinum toxin (Wilcoxon signed rank test); in contrast the changes after normal saline were not significant ($p > 0·5$).

Relief of pain and subjective improvement are summarised in table II. Significant ($p < 0·05$) improvement was observed objectively (obtained by the clinical scoring protocol) and subjectively (from patient's history). Pain relief was also significant ($p < 0·02$).

TABLE II—IMPROVEMENT AFTER INJECTIONS

| — | Improvement | | |
|---|---|---|---|
| | Objective | Subjective | Pain |
| Botulinum-A toxin | 12* (n = 19) | 10* (n = 19) | 14† (n = 16) |
| Normal saline | 7 (n = 20) | 3 (n = 20) | 4 (n = 17) |

*$p < 0·05$.
†$p < 0·02$.

TABLE III—SIDE-EFFECTS ASSOCIATED WITH ACTIVE TREATMENT AND PLACEBO

| Patient | Botulinum toxin | Normal saline |
|---|---|---|
| 1 | Neck sore for 1 day | " |
| 2 | " | Chills for 1 day |
| 3 | Pain at injection site 1 day | |
| 4 | " | Neck weak for 1 day |
| 5 | " | Generally weak 1 day |
| 6 | Stiff neck for 1 day | Mild headache 1 day |
| 7 | Slightly weak neck 2 days | Local soreness 1 day |
| 8 | " | Pain in back 1 day |
| 9 | " | Sleepy for 1 day |
| 10 | Slightly weak neck 1 day | Dizzy for 1 day |

*Side-effects*

The side-effects reported by the patients are summarised in table III.

## Discussion

The clinical scale used here is a slightly modified version of that described in our pilot study,[12] in which there was good intra-observer consistency of scoring.[9] The inter-observer correlation studied here showed that our scale gives reproducible results. It may be applied to the quantification of torticollis in any therapeutic investigation.

The dose of botulinum toxin per muscle was 50 mouse units (20 ng), and in most of the patients this was sufficient to produce weakness and apparent reduction of muscle bulk lasting up to 3 months. It seems that a satisfactory dose for each muscle is in the region of 50 units. Objective and subjective improvements, including pain relief, were achieved in most patients.

Side-effects were reported more commonly in the placebo phase than in the toxin phase, though in the former complaints were generally non-specific and in the latter more indicative of mild neck weakness for 1–2 days. It seems likely, therefore, that botulinum toxin injection, at a total dose of 100 mouse units, will be free of significant systemic adverse reactions in most patients.

Only 1 of the 19 patients who completed the trial did not respond favourably, and this was the subject with generalised dystonia. There was diffuse and gross muscular hyperactivity around the neck, so injection of two muscles was probably inadequate treatment.

This study demonstrates the short-term efficacy and safety of botulinum-A toxin in the treatment of spasmodic torticollis. Long-term follow-up is needed to determine whether repeated injections result in sustained benefit without the emergence of tolerance or late adverse reactions these questions could be answered by open-label administration.

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*References at foot of next column*

# EVALUATION OF SEROLOGICAL CROSS-REACTIVITY BETWEEN ANTIBODIES TO PLASMODIUM AND HTLV-III/LAV

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*Summary* Serum samples from 460 patients with existing or previous *Plasmodium* infections, high antimalarial antibody titres, and no apparent risk of exposure to human T-lymphotropic virus type III/lymphadenopathy-associated virus (HTLV-III/LAV) were assayed for HTLV-III/LAV antibody; only 1 sample, from a 21-year-old African woman, was strongly reactive by enzyme-linked immunosorbent assay (ELISA) and positive by western blot. Conversely, no sample from 100 HTLV-III/LAV-positive American homosexual men was strongly reactive for antibodies to the four *Plasmodium* species that infect human beings by an indirect fluorescent antibody technique, or for antibodies to *Plasmodium falciparum* by an ELISA technique. Thus, exposure to *Plasmodium* does not result in HTLV-III/LAV seropositivity, and HTLV-III/LAV antibodies are not strongly cross-reactive with malarial antigens.

## Introduction

TESTING for antibodies to the human T-lymphotropic virus type III/lymphadenopathy-associated virus (HTLV-III/LAV) is valuable in surveillance of the acquired immunodeficiency syndrome (AIDS). The specificity of the enzyme-linked immunosorbent assay (ELISA), the test most commonly used for HTLV-III/LAV antibody screening, is therefore very important. Some reports have suggested an association between infection with *Plasmodium*, the causative agent of malaria, and HTLV-III/LAV seropositivity.[1,2] Of 250 healthy adults from rural Zaire, 31 were HTLV-III/LAV-positive by ELISA, and another 30 were on the borderline; HTLV-III/LAV seropositivity correlated with high titres of antibodies to *Plasmodium falciparum*.[1] In a study from Venezuela, the frequency of HTLV-III/LAV seropositivity was higher in patients with *P falciparum* and *P vivax* infections than in healthy blood donors in the same area.[2] No evidence of clinical AIDS was found in either of these populations. Serological cross-reactivity between antimalarial antibodies and HTLV-III/LAV is one possible explanation of these findings.

To determine whether antibodies to *Plasmodium* are cross-reactive with HTLV-III/LAV, we studied serum samples from patients who had well-documented infections with one agent but no apparent risk of exposure to the other.

## Patients and Methods

### *Patients with Plasmodium Infections*

We selected serum samples from 460 patients with existing or previous *Plasmodium* infections and no apparent risk of exposure to HTLV-III/LAV. All had high antimalarial antibody titres as determined by a standard indirect fluorescent antibody technique.[3]

The patients were selected from six different populations. The first group was 78 American travellers whose samples were collected in 1964–1974 during or after acute malarial infections with various *Plasmodium* species. The earliest known case of HTLV-III/LAV seropositivity in the United States occurred in 1978.[4]

In a previous study, samples from 9 of 16 neurosyphilitics with induced *P falciparum* and *P malariae* infections in 1962–1963 were weakly reactive on an HTLV-III/LAV ELISA test, and the serum from 1 was strongly reactive.[1] Samples from 4 of these patients were weakly positive on western blot for the p24 band of HTLV-III/LAV. We selected 31 serum specimens collected during the acute infections of 4 of these patients and tested them for HTLV-III/LAV antibody.

We also analysed specimens collected in 1985 from two African and two South American populations with chronic exposure to malaria and high antimalarial antibody titres. The samples were from 57 African children (aged 1·5–8 years) with severe *P falciparum* infections; 183 parasitaemic, symptom-free African children and adults (0·5–55 years) with chronic exposure to *P falciparum*, *P ovale*, and *P malariae*; 59 South American children with chronic exposure to *P falciparum*, *P vivax*, and *P malariae*; and 52 South American Indian adults living in an area where *P vivax* is endemic. The African populations came from outside the known high-prevalence areas of HTLV-III/LAV seropositivity in Central Africa.

### *Patients with HTLV-III/LAV Infections*

We selected specimens that had been collected in 1982–1984 from 100 American homosexual men. All samples were repeatedly reactive to HTLV-III/LAV by ELISA and positive by western blot. 75 of the men had well-documented AIDS, and 25 were symptom-free. Medical records indicated that none of these patients had acute malarial infections, although blood smears were not examined specifically for *Plasmodium* parasites.

### *Malaria Serology*

All serum samples were assayed for antibodies to *Plasmodium* by a standard indirect fluorescent antibody technique.[3] In a previous study of positive and negative control sera, the sensitivity and specificity of this test were both greater than 95%, when a cut-off titre of 1/64 was used.[5] The specificity approaches 100%, however, if 1/1024 is used as the cut-off titre for *P falciparum* and 1/256 as the cut-off titre for *P vivax*, *P ovale*, and *P malariae*. Thus, titres of less than 1/64 are considered non-reactive; 1/1024 or greater (*P falciparum*) or 1/256 or greater (*P vivax*, *P ovale*, and *P malariae*) strongly reactive; and intermediate titres weakly reactive.

Samples from the 100 HTLV-III/LAV-positive patients were also assayed for antibodies to *P falciparum* by a previously described ELISA technique.[6] An optical density value of 0·3 is the standard cut-off used in our laboratory, but the specificity of the test approaches 100% if the cut-off is 1·0. Thus, specimens with optical density values of less than 0·3 are considered non-reactive; 0·3–1·0 weakly reactive; and greater than 1·0 strongly reactive.

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